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Therapeutic Class Review
Miscellaneous Antiemetics

Overview/Summary

The therapeutic class called the Miscellaneous Antiemetics encompasses four agents and they include aprepitant, dronabinol, nabilone and scopolamine.[1-4] All of these agents are available by the oral route, and dronabinol and oral scopolamine have generic formulations. Aprepitant is available by injection as a prodrug called fosaprepitant, which is rapidly converted to aprepitant following intravenous administration. Scopolamine is also available by the transdermal route.

Aprepitant is a selective, high-affinity antagonist of human substance P/neurokinin-1 (NK_1) receptors.[5,6] Aprepitant has little or no affinity for serotonin, dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Aprepitant is Food and Drug Administration (FDA) approved in combination with other antiemetic agents for the prevention of CINV associated with moderately and highly emetogenic cancer chemotherapy and for the prevention of PONV.

Dronabinol and nabilone are orally active cannabinoids, which have complex effects on the central nervous system, including central sympathomimetic activity.[7,8] Cannabinoid receptors have been discovered in neural tissues and these receptors may play a role in mediating the antiemetic effects of dronabinol, nabilone and other cannabinoids. Dronabinol and nabilone are FDA approved for the treatment of CINV in patients who have failed to respond to conventional antiemetic treatments. Dronabinol is also FDA approved for the management of anorexia associated with weight loss in patients with acquired immune deficiency syndrome (AIDS).[7]

Scopolamine, an anticholinergic agent, is a known depressant of the central nervous system which exhibits marked sedative and tranquilizing properties.[2-4,9,10] It exerts its effect by blocking the action of acetylcholine on autonomic receptors innervated by postganglionic cholinergic nerves and smooth muscles that lack cholinergic innervation. Of currently available drugs, scopolamine is considered the single most effective drug in preventing motion sickness-induced nausea and vomiting.[2] Since oral scopolamine has a short duration of action and a high incidence of side effects, oral therapy usually has been reserved for prophylactic treatment of patients exposed to short periods of intense motion or those who are highly susceptible to motion. Antihistamines or other drugs have generally been preferred for the prevention of motion sickness in patients with prolonged exposure to mild-to-moderate motion. The transdermal delivery system of scopolamine is highly effective for the prevention of motion sickness with a longer duration of action and fewer side effects than the oral formulation. Transdermal scopolamine is also effective for the management of PONV and carries this FDA indication.[10]

National and international consensus guidelines recommend the use of aprepitant, along with a type 3 serotonergic ($5\text{-}HT_3$) receptor antagonist plus dexamethasone, as first-line therapy for the prevention of nausea and vomiting induced by moderately and highly emetogenic chemotherapy agents.[15-17] The cannabinoids are reserved for patients who are intolerant or refractory to first-line agents. Scopolamine is considered a treatment option for the management of motion sickness and PONV.[18,19] Consensus guidelines for the management of PONV were published prior to the FDA approval of aprepitant. None of the miscellaneous antiemetics are considered treatment options for the management of nausea and vomiting associated with pregnancy.[20]

Medications

Table 1. Medications Included Within Class Review[1-10]

Generic Name (Trade Name)	Medication Class	Generic Availability
Aprepitant (Emend®)	Miscellaneous Antiemetics	-
Dronabinol (Marinol®)	Miscellaneous Antiemetics	✔
Fosaprepitant (Emend®)	Miscellaneous Antiemetics	-
Nabilone (Cesamet®)	Miscellaneous Antiemetics	-
Scopolamine (Scopace*®, Transderm-Scop®)	Miscellaneous Antiemetics	✔

*Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[4-10]

Generic Name	Chemotherapy-induced Nausea and Vomiting (CINV)	Postoperative Nausea and Vomiting (PONV)	Motion Sickness-related Nausea and Vomiting	Anorexia (AIDS-related)
Aprepitant	✔*	✔		
Dronabinol	✔†			✔
Fosaprepitant	✔*			
Nabilone	✔†			
Scopolamine, oral			✔	
Scopolamine, transdermal		✔	✔	

AIDS=acquired immune deficiency syndrome.
*Prevention of acute and delayed CINV associated with highly emetogenic cancer chemotherapy and prevention of CINV associated with moderately emetogenic cancer chemotherapy.
†Treatment of CINV in patients who have failed to respond adequately to conventional antiemetic treatments.

According to the prescribing information, scopolamine soluble tablets are also used as an anticholinergic central-nervous system depressant, in the symptomatic treatment of postencephalitic parkinsonism and paralysis agitans, in spastic states, and locally as a substitute for atropine in ophthalmology.[9] Scopolamine also inhibits excessive motility and hypertonus of the gastrointestinal tract.

Pharmacokinetics

Following intravenous administration, fosaprepitant is rapidly converted to aprepitant.[6]

Table 3. Pharmacokinetics[4-10]

Generic Name	Time to Peak Concentrations (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aprepitant	3-4	Not reported	0	7 metabolites have been identified (weakly active)	9-13
Dronabinol	1-2.5	4-6 (psychoactive effects), 24 (appetite stimulation)	10-15	1 active metabolite	19-36
Nabilone	<2	8-12	24	Isomeric carbinols	2 (parent), 35 (metabolites)
Scopolamine, oral	Not reported	4-6	<10	None	4.8

Generic Name	Time to Peak Concentrations (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Scopolamine, transdermal	24	72	<10	None	9.5

Clinical Trials[21-47]

The clinical studies outlined in Table 4 support the use of these agents for their Food and Drug Administration (FDA)-approved indications. For the management of chemotherapy-induced nausea and vomiting (CINV), antiemetic treatment regimens that add aprepitant to a 5-HT_3 receptor antagonist plus dexamethasone have been shown to be more effective than regimens that utilize only a 5-HT_3 receptor antagonist plus dexamethasone in providing complete response (no vomiting and no use of rescue therapy) in both the acute and delayed phases of vomiting in patient receiving highly emetogenic chemotherapy.[21-29] Clinical studies comparing the use of aprepitant to ondansetron for the prevention of postoperative nausea and vomiting (PONV) reported similar efficacy for the primary end point of complete response (no vomiting and no use of rescue medications) during the first 24 hours, but aprepitant provided greater protection against vomiting up to 48 hours after surgery.[35,36]

Meta-analyses and head-to-head trials have shown that the cannabinoids were more effective than placebo and some trials reported that they were more effective than prochlorperazine and metoclopramide.[30-34] In a small study, Meiri et al reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV but that combination therapy with these 2 agents was not more effective than either agent alone.[32] There are no published clinical trials comparing dronabinol to nabilone for CINV. Studies evaluating the efficacy of dronabinol for stimulating appetite and promoting weight gain in patients with acquired immune deficiency syndrome (AIDS) have reported modest results with megestrol shown to be more effective.[44-47]

Several clinical studies reported that transdermal scopolamine was effective in the prevention of PONV.[38-41] A few studies reported that premedication with transdermal scopolamine was as effective as droperidol or ondansetron in preventing nausea and vomiting in the early and late postoperative periods but was more likely to produce a dry mouth. With regards to motion sickness, a meta-analysis of 14 studies enrolling over 1,000 patients reported that scopolamine was more effective than placebo in the prevention of motion sickness symptoms.[43] Limited head-to-head studies suggested that scopolamine is at least as effective as antihistamines and more effective than methscopolamine as a preventative agent.[42,43] Dry mouth was more likely with scopolamine than placebo, antihistamines and methscopolamine.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting (CINV)				
Herrstedt et al[21] APR 125 mg, OND 8 mg and DEX 12 mg before chemotherapy and OND 8 mg 8 hours later on day 1; APR 80 mg DAILY on days 2-3 vs control regimen of OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hours later on day 1; OND 8 mg BID on days 2-3	DB, DD, MC, PRO, RCT Patients with breast carcinoma naive to emetogenic chemotherapy and treated with cyclophosphamide alone or with doxorubicin or epirubicin	N=866 3 days of treatment during cycles 1 to 4 of chemotherapy	Primary: Proportion of patients with a complete response (no emesis or use of rescue therapy) in cycle 1, efficacy end points for the multiple-cycle extension were the probabilities of a complete response in cycles 2-4 and a sustained complete response rate across multiple cycles Secondary: Not reported	Primary: 744 patients (85.9%) entered the multiple-cycle extension, and 650 patients (75.1%) completed all 4 cycles. Overall, the complete response was greater with the APR regimen over the 4 cycles: 50.8% versus 42.5% for cycle 1, 53.8% versus 39.4% for cycle 2, 54.1% versus 39.3% for cycle 3, and 55.0% versus 38.4% for cycle 4. The cumulative percentage of patients with a sustained complete response over all 4 cycles was greater with the APR regimen (*P*=0.017). The APR regimen was more effective than a control regimen for the prevention of nausea and emesis induced by moderately emetogenic chemotherapy over multiple chemotherapy cycles. Secondary: Not reported
Gralla et al[22] APR 125 mg, OND 32 mg and DEX 12 mg on day 1; APR 80 mg and DEX 8 mg DAILY on days 2-3; and DEX 8 mg DAILY on day 4 vs control regimen of OND 32 mg IV and DEX 20 mg PO on day 1;	DB, PG, RCT Pooled data from two identically designed studies Cisplatin-naive patients >18 years old receiving their first cisplatin-based chemotherapy	N=1,043 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Complete response (no vomiting and no rescue therapy) on days 1-5 Secondary: Not reported	Primary: In the total combined study population regardless of treatment group or use of concomitant chemotherapy, complete response was achieved in 58% (n=602) of patients. Analysis by treatment group showed 20% greater efficacy with the aprepitant regimen (68% vs 48%; *P*<0.001). Among the approximately 13% (n=142) of patients (n=81 for APR; n=80 for control) who received additional emetogenic chemotherapy (doxorubicin or cyclophosphamide), the aprepitant regimen provided a 33% improvement in the complete response

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DEX 8 mg BID on days 2-4				rate compared with the control regimen (*P*<0.001). Secondary: Not reported
Warr et al[23] APR 125 mg, OND 8 mg and DEX 12 mg before chemotherapy and OND 8 mg 8 hours later on day 1; APR 80 mg DAILY on days 2-3 vs control regimen of OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hours later on day 1; OND 8 mg BID on days 2-3	DB, DD, PG, PRO, RCT Breast cancer patients naive to emetogenic chemotherapy and treated with a regimen of cyclophosphamide alone, cyclophosphamide plus doxorubicin, or cyclophosphamide plus epirubicin	N=857 3 days of treatment, patients observed for 120 hours after initiation of chemotherapy in cycle 1	Primary: Proportion of patients with complete response (no vomiting and no use of rescue therapy) 120 hours after initiation of chemotherapy in cycle 1 Secondary: Proportion of patients with an average item score higher than 6 of 7 on the Functional Living Index-Emesis questionnaire	Primary: Overall complete response was greater with the aprepitant regimen than with the control regimen (50.8% vs 42.5%; *P*=0.015). Secondary: More patients in the aprepitant group reported minimal or no impact of CINV on daily life (63.5% vs 55.6%; *P*=0.019). Both treatments were generally well tolerated. The aprepitant regimen was more effective than the control regimen for prevention of CINV in patients receiving both an anthracycline and cyclophosphamide.
Hesketh et al[24] APR plus OND and DEX on day 1; APR and DEX on days 2-3; DEX on day 4 vs standard therapy of OND and DEX on day 1; DEX on days 2-4	DB, MC, PG, RCT Patients receiving cisplatin ≥70 mg/m^2 for the first time	N=530 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Complete response (no emesis and no rescue therapy) on days 1 to 5 post cisplatin Secondary: Not reported	Primary: The percentage of patients with complete response on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n=260] vs 52.3% in the standard therapy group [n=260]), as were the percentages on day 1, and especially on days 2 to 5 (*P*<0.001 for all three comparisons). Compared with standard dual therapy, addition of aprepitant was generally well tolerated and provided consistent protection against CINV in patients receiving highly emetogenic cisplatin-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				based chemotherapy. Secondary: Not reported
De Wit et al[25] APR 125 mg, OND 32 mg IV and DEX 12 mg on day 1; APR 80 mg and DEX 8 mg on days 2-3; DEX 8 mg on day 4 vs standard group received OND 32 mg IV and DEX 20 mg on day 1; DEX 8 mg BID on days 2-4	DB, MC, RCT Cancer patients receiving a first cycle of cisplatin-based ≥70 mg/m^2) chemotherapy	N=1,038 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Combined exploratory endpoint of no emesis and no significant nausea (ie, nausea which interfered with a patient's normal activities) over the 5 days following cisplatin, for up to six cycles of chemotherapy Secondary: Not reported	Primary: In every cycle, the estimated probabilities (rates) of no emesis and no significant nausea were significantly higher (*P*<0.006) in the aprepitant group: in the first cycle, rates were 61% in the aprepitant group (n=516) and 46% in the standard therapy group (n=522), and thereafter, rates for the aprepitant regimen remained higher throughout (59% [n=89] versus 40% [n=78] for the standard therapy, by cycle 6). Repeated dosing with aprepitant over multiple cycles was generally well tolerated. Those who received aprepitant in addition to standard therapy had consistently better antiemetic protection that was well maintained over multiple cycles of highly emetogenic chemotherapy. Secondary: Not reported
Poli-Bigelli et al[26] APR 125 mg, OND 32 mg IV and DEX 12 mg PO on day 1; APR 80 mg and DEX 8 mg PO DAILY on days 2-3; DEX 8 mg PO on day 4 vs standard therapy of OND 32 mg IV and DEX 20 mg PO on day 1; DEX 8 mg PO BID on days 2-4	DB, MC, PG, RCT Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy	N=1,091 4 days of treatment and looking at a response 120 hours after chemotherapy	Primary: Primary endpoint was complete response (no emesis and no rescue therapy) during the 5-day period post cisplatin Secondary: Not reported	Primary: During the 5 days after chemotherapy, the percentages of patients who achieved a complete response were 62.7% in the aprepitant group (163 of 260 patients) versus 43.3% in the standard therapy group (114 of 263 patients; *P*<0.001). For day 1, the complete response rates were 82.8% for the aprepitant group and 68.4% for the standard therapy group (*P*<0.001); for days 2-5, the complete response rates were 67.7% in the aprepitant group and 46.8% in the standard therapy group (*P*<0.001). The overall incidence of adverse events was similar between the 2 treatment groups (72.8% in the aprepitant group [206 of 283 patients] and 72.6% in the standard therapy group [207 of 285 patients]) as were rates of serious adverse events,

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				discontinuations due to adverse events, and deaths. In patients with cancer who were receiving high-dose cisplatin-based chemotherapy, therapy consisting of APR (125 mg on day 1 and 80 mg on days 2-3) plus a standard regimen of OND and DEX provided greater antiemetic protection compared with standard therapy alone and was generally well tolerated. Secondary: Not reported
Martin et al[27] APR and DEX plus OND on day 1; APR and DEX on days 2-5 vs standard antiemetic therapy of DEX and OND on day 1; DEX on days 2-5	DB, RCT Patients treated with cisplatin	N=381 5 days of treatment, Functional Living Index-Emesis was completed on day 6	Primary: The Functional Living Index-Emesis Secondary: Not reported	Primary: Compared with standard therapy, significantly more patients treated with the high-dose APR regimen achieved a complete response (71% vs 44%; *P*<0.001) and also reported no impact on daily life as indicated by the Functional Living Index-Emesis total score (84% vs 66%; *P*<0.01). Use of the Functional Living Index-Emesis demonstrated that improved control of emesis was highly effective in reducing the impact of CINV on patients' daily activities. Secondary: Not reported
Schmoll et al[28] APR 125 mg PO, OND 32 mg IV and DEX 12 mg PO before chemotherapy; APR 80 mg DAILY and DEX 8 mg DAILY on days 2-3; DEX 8 mg DAILY on day 4 vs control regimen of OND 32 mg IV and DEX 20 mg before chemotherapy on day 1; OND 8	DB, PC, PG, RCT Cisplatin-naïve patients with solid malignancies scheduled to receive cisplatin ≥70 mg/m^2 in cycle 1	N=489 5 days	Primary: Proportion of patients with complete response (no vomiting and no use of rescue therapy) in the overall phase (days 1-5) Secondary: Proportion of	Primary: Complete response rates were higher in the APR than control group in the overall phase of days 1-5 (72% vs 61%; *P*=0.003). Secondary: Complete response rates were higher in the APR than control group in the acute (88% vs 79%; *P*=0.005) and delayed phases (74% vs 63%; *P*=0.004). Rates of no vomiting were higher in the APR than control group in the overall (77% vs 62%; *P*≤0.001) acute (89% vs 81%; *P*=0.004) and delayed phases (79% vs 64%; *P*≤0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg BID and DEX 8 mg BID on days 2-4			patients with complete response in acute (day 1) and delayed phase (days 2-5), no vomiting in the overall phase, no vomiting in the delayed phase	Rates of no rescue therapy were similar between groups. The overall incidences and profiles of clinical and laboratory adverse experiences were similar between the treatment regimens. Although the incidence of drug-related laboratory adverse events was slightly higher in the APR group, there was no clinically meaningful difference between groups in the incidence of any specific event.
Herrington et al[29] APR 125 mg PO, PAL 0.25 mg IV and DEX 12 mg PO prior to chemotherapy on day 1; APR 80 mg and DEX 8 mg PO on days 2-3; DEX 8 mg PO on day 4 (Arm A) vs APR 125 mg PO, PAL 0.25 mg IV and DEX 12 mg PO prior to chemotherapy on day 1; DEX 8 mg PO on days 2-4 (Arm B) vs PAL 0.25 mg IV and DEX 18 mg PO prior to chemotherapy on day 1; DEX 8 mg PO on days 2-4 (Arm C)	DB, PC, RCT Patients ≥18 years receiving highly emetogenic regimens of cisplatin ≥50 mg/m^2 or breast cancer regimens that included anthracycline or cyclophosphamide; patients who had received prior chemotherapy could not have greater than grade 1 nausea	N=75 5 days	Primary: Proportion of patients with acute (day 1) and delayed emesis (days 2-5) Secondary: Prevention of acute and delayed nausea, use of breakthrough antiemetics	Primary: The proportion of patients without emesis during the first 24 hours was similar between Arms A and B (96.4% vs 100%, respectively; *P*=1.00). The proportion of patients without delayed emesis was similar between Arms A and B (92.9% vs 92.6%, respectively; *P*=1.00). An interim analysis displayed unacceptable emesis events in Arm C and this group was terminated. Secondary: There were no significant differences between Arms A and B for nausea over days 1-5 (no *P* values reported). There were no significant differences between Arms A and B for the use of breakthrough antiemetics during the acute (81.5% vs 85.2%, respectively; *P*=1.00) or delayed phase (55.6% vs 70.4%, respectively; *P*=0.26). There were no reports of serious adverse events that were related to study medication.
Gilbert et al[30] Metoclopramide (80 mg/m^2 IV loading dose followed by 20	DB, RCT Patients with cancer receiving high dose	N=126 4 days	Primary: Efficacy was measured by the Emetic Process	Primary: The median number of emetic episodes on the metoclopramide study arm were: 1 (0-7, day 6), 1 (0-6, day 5), 2 (0-9, day 4), and 2 (0-10, with dronabinol day 3) or 2 (0-7, no dronabinol day 3)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/m^2/hour) each with either dronabinol 5 mg/m^2 or placebo capsules for two doses before carmustine on the last day of chemotherapy; all subjects received scheduled lorazepam and diphenhydramine throughout the 4-day study period vs 4-day continuous infusion prochlorperazine (6 mg/m^2 IV loading dose followed by 1.5 mg/ m^2/hour)	cisplatin, cyclophosphamide, and carmustine with autologous bone marrow support		Rating Scale and the Rhodes Index of Nausea and Vomiting Form 2 Secondary: Not reported	and on the prochlorperazine study arm were: 4 (0-12, day 6), 0 (0-8, day 5), 0 (0-12, day 4) and 2.5 (0-9, with dronabinol day 3) or 2 (0-12, no dronabinol day 3). Metoclopramide was significantly better on the first day of therapy (day 6; *P*<0.002) and prochlorperazine was significantly better on the third day of therapy (day 4; *P*<0.002). There was no significant difference among any of the four arms on the last day of chemotherapy (day 3), or when the median number of emetic episodes over the total study period was compared. Secondary: Not reported
Lane et al[31] Dronabinol 10 mg every 6 hours plus placebo (group 1) vs placebo plus prochlorperazine 10 mg every 6 hours (group 2) vs dronabinol and prochlorperazine, 10 mg every 6 hours (group 3)	DB, MC, PG, RCT Individuals 18-69 years of age, being treated for cancer with chemotherapy	N=62 Treatment begun 24 hours prior to initiation of chemotherapy and continued for 24 hours after the last dose of chemotherapy	Primary: Duration per episode of vomiting Secondary: Side effects	Primary: The median duration per episode of vomiting was 1 minute in group 3 versus 2 minutes in group 1 and 4 minutes in group 2 (*P*<0.001). Secondary: Side effects, primarily central nervous system, were more common in group 1 than in group 2 (*P*<0.01); addition of prochlorperazine to dronabinol appeared to decrease the frequency of dysphoric effects seen with the latter agent. The combination was significantly more effective than either single agent in controlling CINV (*P*<0.001).
Meiri et al[32] Dronabinol 2.5 mg PO, DEX 20 mg PO and OND 16 mg IV before and dronabinol 2.5 mg after chemotherapy on day 1; dronabinol 10-20 mg on days 2-5	DB, PC, RCT Patients receiving moderately to highly emetogenic chemotherapy	N=64 5 days	Primary: Total response (nausea intensity <5 mm on visual analog scale, no vomiting/retching, no rescue	Primary: Total response was similar with dronabinol (54%), OND (58%), and combination therapy (47%) vs placebo (20%) (no *P* values reported). Nausea absence was significantly greater in the active treatment groups (dronabinol, 71%; OND, 64%; combination therapy, 53%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs dronabinol 2.5 mg PO, DEX 20 mg PO and OND 16 mg IV before and dronabinol 2.5 mg after chemotherapy on day 1; OND 8-16 mg on days 2-5 vs dronabinol 2.5 mg PO, DEX 20 mg PO and OND 16 mg IV before and dronabinol 2.5 mg after chemotherapy on day 1; dronabinol 10-20 mg and OND 8-16 mg on days 2-5 vs placebo, DEX 20 mg PO and OND 16 mg IV before chemotherapy on day 1; placebo on days 2-5			antiemetics), nausea (occurrence and intensity), vomiting/retching episodes Secondary: Not reported	vs placebo (15%; *P*<0.05 for all comparisons). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Active treatments were well tolerated. Secondary: Not reported
Tramer et al[33] Cannabinoids (dronabinol 13 trials, nabilone 16 trials and levonantradol* 1 trial) vs conventional antiemetics (prochloperazine 12 trials, metoclopramide 4 trials, chlorpromazine 2 trials, domperidone* 2 trials, alizapride*	MA of RCT published between 1975 and 1997 (literature search of databases including Medline, Embase and Cochrane library to August 2000) Patients receiving chemotherapy	N=1,366 30 trials (average trial size N=46) 24 hours	Primary: Antiemetic efficacy (absence of nausea or vomiting in the first 24 hours of chemotherapy) Secondary: Number of patients who expressed preference for	Primary; Cannabinoids were more effective antiemetics than prochlorperazine, metoclopramide, chorpromazine, thiethylperazine, haloperidol, domperidone* or alizapride* for complete control of nausea (RR, 1.38; 95% CI, 1.18 to 1.62; NNT 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT 8). Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. Secondary: In crossover trials, patients preferred cannabinoids for future

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1 trial, haloperidol 1 trial and thiethylperazine 1 trial) or placebo (12 trials) (trial may have >1 treatment arm)			cannabis for control for future chemotherapy cycles, adverse effects	chemotherapy cycles (RR, 2.39; 95% CI, 2.05 to 2.78; NNT 3). Side effects that were considered "potentially beneficial" that were observed more frequently in patients receiving cannabinoids were a "high", sedation, drowsiness, and euphoria. Side effects that were considered harmful that were reported more often with cannabinoids were dizziness, dysphoria, depression, hallucinations, paranoia and arterial hypotension. Patients given cannabinoids were more likely to withdraw due to side effects (RR, 4.67; 95% CI, 3.07 to 7.09; NNT 11).
Machado Rocha et al[34] Cannabinoids (dronabinol, nabilone and levonantradol*) vs neuroleptics or placebo	MA of RCT (literature search of databases including Medline, Embase and Cochrane library up to December 2006) Patients with any type of cancer receiving chemotherapy with low, moderate and high emetic potential	N=1,719 30 trials (13 trials were included in the MA of antiemetic efficacy and 18 trials were included in MA for medication preference) Duration not reported	Primary: Antiemetic efficacy (not defined), preference for one of the study drugs, adverse effects Secondary: Not reported	Primary: In terms of antiemetic efficacy, dronabinol was not more effective than placebo (n=185; RR, 0.47; 95% CI, 0.19 to 1.16; *P*=0.10). In terms of antiemetic efficacy, dronabinol was more effective than neuroleptics (n=325; RR, 0.67; 95% CI, 0.47 to 0.96; NNT 3.4). In terms of antiemetic efficacy, nabilone was not more effective than neuroleptics (n=277; RR, 0.88; 95% CI, 0.72 to 1.08; *P*=0.21). Levonantradol* vs neuroleptics (n=194; RR, 0.94; 95% CI, 0.75 to 1.18). Patients preferred cannabinoids over other study drugs (n=1,138; RR, 0.33; 95% CI, 0.24 to 0.44; *P*<0.00001; NNT1.8). The adverse effects were more intense and occurred more often among patients who received cannabinoids.
Postoperative Nausea and Vomiting (PONV)				
Gan et al[35] APR 40 mg PO preoperative vs	DB, PC, MC Patients ≥18 years receiving general anesthesia for open	N=805 48 hours	Primary: Proportion of patients achieving complete response (no	Primary: The proportion of patients who experienced a complete response over 0-24 hours after surgery was not significantly different between APR 40 mg (45%), APR 125 mg (43%) and OND 4 mg (42%; *P*>0.05 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
APR 125 mg PO preoperative vs OND 4 mg IV preoperative	abdominal surgery		vomiting and no use of rescue medications) within 24 hours after surgery Secondary: Incidence of no vomiting 0-24 and 0-48 hours, no rescue therapy 0-24 hours	Secondary: The incidence of no vomiting (0-24 hours) was higher with APR 40 mg (90%) and APR 125 mg (95%) vs OND (74%; *P*<0.001 for both comparisons), although between-treatment use of rescue medications (45%, 44% and 46%, respectively) was not different. Both APR doses had higher incidences of no vomiting over 0-48 hours (*P*<0.001). No statistically significant differences were seen among the side effect profiles of the treatments.
Diemunsch et al[36] APR 40 mg PO preoperative vs APR 125 mg PO preoperative vs OND 4 mg IV preoperative	DB, PC, MC Patients ≥18 years receiving general anesthesia for open abdominal surgery	N=922 48 hours	Primary: Proportion of patients achieving complete response (no vomiting and no use of rescue medications) and no vomiting within 24 hours after surgery Secondary: Incidence of no vomiting 0-48 hours after surgery	Primary: APR at both doses was comparable in efficacy to OND for complete response 0-24 hours after surgery (64% for APR 40 mg, 63% for APR 125 mg and 55% for OND; *P* value not reported). APR at both doses was more effective than OND for no vomiting 0-24 hours after surgery (84% for APR 40 mg, 86% for APR 125 mg and 71% for OND; *P*<0.001). Secondary: APR at both doses was more effective than OND for no vomiting 0-48 hours after surgery (82% for APR 40 mg, 85% for APR 125 mg and 66% for OND; *P*<0.001). The distribution of peak nausea scores was lower in both APR groups vs OND (*P*<0.05).
Layeeque et al[37] Prophylactic oral dronabinol 5 mg and rectal prochlorperazine 25 mg (after anesthesia) vs	RETRO Patients operated on before September 1, 2002, who received standard preoperative care were designated	N=242 RETRO review of all patients between July 2001 and	Primary: Rate and severity of PONV Secondary: Not reported	Primary: The rate of nausea and vomiting were significantly better in the patients treated prophylactically with dronabinol and prochlorperazine (59% vs 15%; *P*<0.001 and 29% vs 3%; *P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
standard preoperative care (which does not include routine prophylaxis with antiemetics)	as the "old cohort"; patients operated on after September 1, 2002, who received prophylactic oral dronabinol 5 mg and rectal prochlorperazine 25 mg were designated as the "new cohort"	November 2002		Not reported
White et al[38] Scopolamine transdermal patch (applied 60 minutes before entering the operating room and removed on the third postoperative day) vs droperidol 1.25 mg IV or OND 4 mg IV (administered near the end of the procedure) All patients received dexamethasone 4 mg IV after induction of anesthesia.	DB, MC, PC Patients 18-65 years undergoing major laparoscopic (scopolamine vs OND) or plastic surgery (scopolamine vs droperidol)	N=150 3 days	Primary: Incidence of nausea or vomiting, need for rescue antiemetics, proportion of patients achieving complete response (absence of protracted nausea or repeated episodes of vomiting/retching requiring rescue antiemetics) 0-72 hours after surgery, side effects Secondary: Not reported	Primary: In the plastic surgery study, there were no significant differences between scopolamine and droperidol groups with respect to the incidence PONV and the need for antiemetic rescue medication during the 72-hour follow-up period. Complete response rates were 41% for both scopolamine and droperidol. Dry mouth occurred significantly more frequently in the scopolamine group (25% vs 6%; $P<0.05$); however, there was no difference in the frequency of restlessness (9% vs 12%), visual disturbances (19% vs 15%) or drowsiness (19% vs 18%) between scopolamine and droperidol. In the laparoscopic surgery study, there were no significant differences between scopolamine and OND with respect to the incidence of PONV and the need for antiemetic rescue medications during the 72-hour study period. The complete response rates did not differ significantly between scopolamine (47%) and OND (51%). Dry mouth was reported more frequently with scopolamine than OND (18% vs 5%, respectively); however, the incidence of headache (11% vs 13%, respectively), restlessness (11% vs 8%, respectively) and drowsiness (13% vs 10%, respectively) were similar between the 2 treatment groups (no *P* values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Harnett et al[39] Scopolamine transdermal patch vs OND 4 mg IV vs placebo All study drugs were administered at time of cord clamping.	DB, RCT Women undergoing cesarean delivery under spinal anesthesia	N=240 24 hours	Primary: Incidence of all emesis 0-24 hours after surgery Secondary: Incidence of antiemetic use	Primary: Overall emesis rates were 40.0%, 41.8% and 59.3% for the scopolamine, OND and placebo groups, (P=0.025). The greatest reduction in emesis in the scopolamine group when compared with placebo was in the 6-24 hour time period. Secondary: Rescue antiemetics were used in 35%-45% of patients overall in the first 24 hours. There was a trend toward less use in the scopolamine group compared to placebo at 2-6 hours and 6-24 hours after surgery (0.05<P< 0.1). Dry mouth was more commonly seen in the scopolamine group in the 6-24 hour interval than OND or placebo (19%, 4% and 9%, respectively; P<0.05 vs placebo).
Jones et al[40] Scopolamine transdermal patch vs placebo All patients received prophylactic ondansetron IV.	DB, PC, PRO, RCT Patients 18 years or older at high risk for PONV	N=56 Patients administered a patch prior to surgery and monitored for 72 hours following surgery	Primary: Incidence and severity of PONV, side effects, antiemetic requirements Secondary: Not reported	Primary: Patients in the scopolamine group had a lower incidence of PONV (P=0.043), longer time to first reported nausea (P=0.044), longer time to first episode of emesis (P=0.031), and decreased supplemental antiemetic requirements (P=0.016) compared with the placebo group. Secondary: Not reported
Tarkkila et al[41] Combination of promethazine and transdermal scopolamine (1.5 mg) vs oral diazepam (5-15 mg) plus oral promethazine (10 mg)	DB, PRO Patients scheduled for arthroplasty surgery of the lower extremity were anaesthetized with spinal anesthesia with a combination of isobaric bupivacaine	N=60 24 hours	Primary: Effect of different premedications on postoperative emetic sequelae induced by intrathecal morphine Secondary:	Primary: 60% of the patients with both promethazine and transdermal scopolamine were totally free from PONV symptoms compared to those premedicated with diazepam (40%) or promethazine alone (30%). Promethazine together with transdermal scopolamine significantly reduced the number of patients with vomiting (to 25%) and also vomiting episodes. This combination was also more efficient in reducing the incidence of nausea (to 25%) and nausea episodes

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	20 mg and morphine 0.3 mg		Not reported	than promethazine alone (P<0.05). PONV occurred in a majority of patients during the first 12 hours of the 24-hour study period and the need for additional analgesics thereafter. Secondary: Not reported
Motion Sickness – Nausea				
Dahle et al[42] Scopolamine transdermal patch (0.5 mg) vs meclizine 25 mg tablet vs placebo	DB, DD, PC, RCT, XO Individuals between the ages of 20 to 39 years, no concomitant medication use that could influence trial outcome, no recent travel by air or sea	N=36 Each subject went through 3 times with 70 hours between experiments	Primary: Self-reported nausea score, mean motion sickness score, adverse reactions Secondary: Not reported	Primary: Mean motion sickness scores were highest during the placebo period and decreased with the use of scopolamine and meclizine. There was a significant difference between the scopolamine and placebo groups, the scopolamine and meclizine groups, but not the meclizine and placebo groups (no P values provided). However there was a statistical difference between meclizine and placebo for the last half of the trial period (no P value provided). The number of patients experiencing dry mouth was 21 for the scopolamine groups, 8 for placebo, and 6 for meclizine (P value not provided). Secondary: Not reported
Spinks et al[43] Scopolamine transdermal patches, tablets, capsules, oral solutions or intravenously vs placebo, antihistamines (cinnarizine*, dimenhydrinate, meclizine, promethazine) and other drugs (calcium channel antagonists, lorazepam, methscopolamine)	MA Review of RCT, published in MEDLINE (1966-May 2007), EMBASE (1974-May 2007), OVID (1982-May 2007)	N=1,025 14 trials Duration varied	Primary: Prevention and treatment clinically defined motion sickness Secondary: Task ability and psychological tests, and adverse effects	Scopolamine was more effective than placebo in the prevention of motion sickness symptoms (RR, 0.47; 95% CI, 0.31 to 0.71). Transdermal scopolamine was more effective than methscopolamine in preventing motion sickness (RR, 0.33; 95% CI, 0.09 to 1.19). Compared to meclizine, scopolamine showed a decrease in mean motion sickness score (89%) than meclizine (59%) (no P value reported), and delayed the onset of symptoms for longer than meclizine (mean time and percentage increase from baseline: 4.32 minutes [32.47%] with scopolamine vs 0.58 seconds [8.66%] with meclizine). Transdermal scopolamine was equivalent to other antihistamines such as promethazine and dimenhydrinate in preventing motion sickness. Studies comparing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs combination of scopolamine with ephedrine, cyclizine or placebo				the effectiveness of scopolamine with cinnarizine* produced mixed results. When scopolamine alone or in combination with ephedrine was studied, the meta-analysis showed no statistically significant results, although fewer participants treated with scopolamine alone reported symptoms (RR, 0.70; 95% CI, 0.39 to 1.26). Scopolamine was more effective at delaying the onset of motion sickness than lorazepam, which was found to hasten the onset of symptoms: mean time and percentage change from baseline: 4.32 minutes (32.47%) with scopolamine compared with –1.35 minutes [–1.65%] with lorazepam. Secondary: There was no marked difference in performance (task ability and psychological tests) between scopolamine and placebo (no *P* values reported). Scopolamine was no more likely to induce drowsiness (RR, 1.42; 95% CI, 0.79 to 2.56; *P* value not reported), dizziness (10%-27% vs 0%-26%; no *P* value reported) or blurring of vision (RR, 2.73; 95% CI, 0.89 to 8.37; *P*=0.08) than placebo. Scopolamine (35%-50%) was associated with more reports of dry mouth than placebo (5%), dimenhydrinate (0%) and methscopolamine (10%). No studies were available relating to the therapeutic effectiveness of scopolamine in the management of established symptoms of motion sickness.
Anorexia (Acquired Immune Deficiency Syndrome-Related)				
Beal et al[44] Dronabinol 2.5 mg BID vs	DB, MC, PC, PG AIDS-related anorexia and ≥2.3 kg weight loss	N=139 6 weeks	Primary: Patients rated appetite, mood, and nausea by using a 100-mm visual analogue	Primary: Dronabinol was associated with increased appetite above baseline (38% vs 8% for placebo; *P*=0.015), improvement in mood (10% vs –2%; *P*=0.06), and decreased nausea (20% vs 7%; *P*=0.05). Weight was stable in dronabinol patients, while placebo recipients had a mean loss of 0.4 kg (*P*=0.14). Of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			scale 3 days weekly Secondary: Side effects	dronabinol patients, 22% gained ≥2 kg, compared with 10.5% of placebo recipients (*P*=0.11). Secondary: Side effects were mostly mild-to-moderate in severity (euphoria, dizziness, thinking abnormalities); there was no difference in discontinuation of therapy between dronabinol (8.3%) and placebo (4.5%) recipients.
Struwe et al[45] Dronabinol 5 mg BID for 5 weeks followed by a two week washout period vs placebo for 5 weeks followed by a two week washout period	DB, PC, RCT HIV-infected patients who had at least a 2.25 kg weight loss	N=12 7 weeks	Primary: Caloric intake, weight, percent body fat, serum prealbumin, and symptom distress Secondary: Not reported	Primary: During dronabinol treatment, subjects experienced increased percent body fat (1%; *P*=0.04); decreased symptom distress (*P*=0.04); and trends toward weight gain (0.5 kg; *P*=0.13), increased prealbumin (29.0 mg/L; *P*=0.11), and improved appetite score (*P*=0.14). Secondary: Not reported
Jatoi et al[46] Dronabinol 2.5 mg BID plus placebo vs megestrol acetate 800 mg/day liquid suspension plus placebo vs dronabinol 2.5 mg BID and megestrol acetate 800 mg/day liquid suspension	DB, MC, RCT Adult patients (>18 years of age) with histologic evidence of an incurable malignancy other than brain, breast, ovarian, or endometrial cancer	N=469 Patients completed a baseline questionnaire and at least one weekly questionnaire in the first follow-up	Primary: Binary end points of whether patients' appetite improved and whether patients gained 10% of their baseline weight at some point during the study Secondary: Not reported	Primary: A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared with dronabinol-treated patients: 75% versus 49% (*P*=0.0001) for appetite and 11% versus 3% (*P*=0.02) for ≥10% baseline weight gain. Combination treatment resulted in no significant differences in appetite or weight compared with megestrol acetate alone. Secondary: Not reported
Timpone et al[47] Dronabinol 2.5 mg BID (D)	MC, RCT Patients with HIV	N=52 12 weeks	Primary: Occurrence of adverse events,	Primary: Occurrence of adverse events, drug discontinuation, new AIDS-defining conditions, or CD4+ T lymphocyte changes was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs megestrol acetate 750 mg/day (M750) vs dronabinol 2.5 mg BID and megestrol acetate 750 mg/day (M750+D) vs dronabinol 2.5 mg BID and megestrol acetate 250 mg/day (M250+D)	wasting syndrome		drug discontinuation, new AIDS-defining conditions, CD4+ T lymphocyte, mean weight change, C_{max}, AUC, and visual analog scale for hunger score Secondary: Not reported	statistically significantly different among arms. Serious adverse events assessed as related to dronabinol included central nervous system events and those assessed as related to megestrol acetate included dyspnea, liver enzyme changes, and hyperglycemia. The mean weight change +/- SE over 12 weeks was as follows: D, –2.0 +/- 1.3 kg; M750, +6.5 +/- 1.1 kg; M750+D, +6.0 +/- 1.0 kg; and M250+D, –0.3 +/- 1.0 kg (difference among treatment arms; *P*=0.0001). Pharmacokinetic parameters measured after 2 weeks of therapy for M750 were C_{max}=985 ng/ml and AUC=22,487 ng x hour/mL, and for dronabinol and its active metabolite (HO-THC), respectively, were C_{max}=2.01; 4.61 ng/mL and AUC=5.3; 23.7 ng x hour/mL. For megestrol acetate, but not dronabinol, there was a positive correlation at week 2 between both C_{max} and AUC with each of the following: (1) weight change, (2) breakfast visual analog scale for hunger score, and (3) dinner visual analog scale for hunger score. Secondary: Not reported

*Product not available in the United States
Drug regimen abbreviations: APR=aprepitant, BID=twice daily, DEX=dexamethasone, IV=intravenous, OND=ondansetron, PAL=palonosetron, PO=by mouth
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multi-center, NNT=numbers needed to treat, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SE=standard error, XO=cross over
Miscellaneous abbreviations: AIDS=acquired immune deficiency syndrome, AUC=area under the curve, CINV=chemotherapy-induced nausea and vomiting, C_{max}=maximum concentration, HIV=human immunodeficiency virus, PONV=postoperative nausea and vomiting

Special Populations

Table 5. Special Populations[4-14]

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
Aprepitant	No dosage adjustment required in elderly. Not studied in pediatric population.	No dosage adjustment required.	No dosage adjustment required for mild-to-moderate hepatic insufficiency; not studied in severe disease.	B	Unknown.	
Dronabinol	Caution advised in elderly. Not studied for AIDS-related anorexia in pediatric population.	No dosage adjustment required.	Dosage adjustment required for severe liver failure.	C	Yes (% not reported).	Caution advised for patients with cardiac, psychiatric, or seizure disorders or history of substance abuse.
Nabilone	Caution advised in elderly. Not studied in pediatric population.	Population not studied.	Population not studied.	C	Unknown.	Caution advised for patients with cardiac or seizure disorders, history of substance abuse, mania, depression or schizo-phrenia.
Scopol-amine, oral	Caution advised in elderly. Not studied in pediatric population.	Contraindica-tion.	Contraindica-tion.	C	Unknown.	Caution advised for patients with cardiac disease.
Scopol-amine, trans-dermal	Caution advised in elderly. Not recom-mended in children.	Caution advised.	Caution advised.	C	Yes (% not reported).	Caution advised for patients with intestinal, pyloric or urinary bladder neck

Generic Name	Population and Precaution					
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk	Other
						obstruction; or history of seizure or psychosis.

AIDS=acquired immune deficiency syndrome

Adverse Drug Events

The most frequently reported adverse effects for the miscellaneous antiemetics are summarized in Table 6. Patients receiving treatment with dronabinol, nabilone and scopolamine should be cautioned about performing tasks which require mental alertness until it is established that they are able to tolerate the drug and to perform such tasks safely.[7-10] Rarely, idiosyncratic reactions, such as acute toxic psychosis, may occur at regular therapeutic doses of scopolamine.[9,10]

Table 6. Adverse Drug Events[4-14]

Adverse Event(s)	Aprepitant	Dronabinol	Nabilone	Scopolamine
Cardiovascular				
Bradycardia	4	-	-	-
Hypertension	-	✔	-	-
Hypotension	≤6	✔	8	-
Palpitations	-	✔	-	-
Syncope	-	✔	-	-
Tachycardia	-	✔	✔	✔ PO
Central Nervous System				
Abnormal thinking	-	3-10	-	-
Amnesia	-	✔	-	-
Anxiety	-	✔	✔	-
Ataxia	-	✔	13-14	-
Confusion	-	✔	2	-
Depression	-	-	14	-
Detachment	-	✔	2	-
Difficulty concentrating	-	-	12	-
Dizziness	3-7	3-10	59	12 TD
Drowsiness	-	-	52-66	✔ PO, <17 TD
Dysphoria	-	-	9	-
Euphoria	-	8-24	11-38	-
Fatigue	18-22	-	-	-
Hallucinations	-	✔	✔	-
Headache	9-16	-	6-7	-
Paranoia	-	3-10	-	-
Sedation	-	3-10	3	-
Seizures	-	✔	✔	-
Sleep disturbance (includes insomnia)	3-4	-	11	-
Psychosis	-	-	✔	-
Vertigo	-	-	52-59	-
Dermatological				
Dry skin	-	-	-	✔ PO
Gastrointestinal				
Abdominal pain	5	3-10	-	-
Anorexia	4-10	-	8	-

Adverse Event(s)	Aprepitant	Dronabinol	Nabilone	Scopolamine
Appetite increased	-	-	2	-
Constipation	9-12	-	-	-
Diarrhea	6-10	-	-	-
Dry mouth	-	-	22-36	✔ PO, 29-67 TD
Dyspepsia	8	-	-	-
Epigastric discomfort	4	-	-	-
Gastritis	4	-	-	-
Mucous membrane disorder	3	-	-	-
Nausea	7-13	3-10	4	-
Stomatitis	5	-	-	-
Throat pain	3	-	-	-
Vomiting	3-8	3-10	-	-
Hematologic				
Hemoglobin decreased	2-5	-	-	-
Leukopenia	9	-	-	-
Neutropenia	3-9	-	-	-
Laboratory Test Abnormalities				
Elevated ALT	1-6	-	-	-
Elevated AST	3	-	-	-
Elevated BUN	5	-	-	-
Elevated serum creatinine	4	-	-	-
Proteinuria	7	-	-	-
Musculoskeletal				
Asthenia	3	✔	-	-
Weakness	3-18	✔	8	-
Other				
Alopecia	24	-	-	-
Blurred vision/visual disturbance	-	-	13	✔
Dehydration	6	-	-	-
Hiccups	11	-	-	-
Flushing	3	✔	-	✔ PO
Mydriasis	-	-	-	✔ PO
Tinnitus	4	-	-	-
Urinary retention	-	-	-	✔ PO

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood nitrogen urea, PO=oral, TD=trandermal
✔ Percent not specified.
- Event not reported or incidence <1%.

Contraindications / Precautions

Aprepitant is a weak-to-moderate (dose-dependent) cytochrome P450 isoenzyme 3A4 inhibitor and is contraindicated in patients receiving astemizole, cisapride, pimozide and/or terfenadine (see Drug Interactions section for more information).[5,6] Dronabinol and nabilone are contraindicated in patients with a history of hypersensitivity to any cannabinoid.[7,8] Dronabinol is also contraindicated in patients with an allergy to sesame oil. Both oral and transdermal scopolamine are contraindicated in patients with angle-closure (narrow angle) glaucoma.[9,10] Patients with chronic open-angle (wide-angle) glaucoma should be carefully monitored as the mydriatic effect of scopolamine may cause an increase in intraocular pressure. Oral scopolamine is also contraindicated in patients with prostatic hypertrophy, pyloric obstruction, impaired renal or hepatic function.[9]

Nabilone (Schedule CII) and dronabinol (Schedule CIII) are regulated under the Controlled Substances Act and should be used with caution in patients with a history of substance abuse.[7,8] Both psychological and physiological dependence have been noted in healthy individuals receiving dronabinol.[7] An

abstinence syndrome has been reported after abrupt discontinuation of dronabinol in volunteers who were receiving high dosages for 12-16 consecutive days. It is not known at this time if nabilone causes physical dependence.[8]

Drug Interactions

Aprepitant is a weak-to-moderate (dose-dependent) cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor and is contraindicated in patients receiving astemizole, cisapride, pimozide and/or terfenadine.[5,6] Concurrent administration with these drugs could result in elevated plasma concentrations, potentially causing serious or life-threatening reactions. Since aprepitant is a substrate for CYP3A4, coadministration with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Dronabinol, nabilone and scopolamine should be used with caution in patients receiving concomitant therapy with sedatives, hypnotics, or other psychoactive substances because of the potential for additive or synergistic central nervous system effects.[7-10] Dronabinol and nabilone are highly bound to plasma proteins and may displace other protein-bound drugs.[7,8]

Table 7. Drug Interactions[3-14]

Generic Name	Interacting Medication or Disease	Potential Result
Aprepitant	Astemizole	Aprepitant may inhibit the metabolism of this drug. Concurrent use is contraindicated.
Aprepitant	Cisapride	Aprepitant may inhibit the metabolism of this drug. Concurrent use is contraindicated.
Aprepitant	Clarithromycin, diltiazem, itraconazole, ketoconazole, nefazodone, ritonavir and nelfinavir	Aprepitant is a substrate for cytochrome P450 3A4. Coadministration of aprepitant with strong CYP3A4 inhibitors and/or diltiazem (moderate CYP3A4 inhibitor) should be approached with caution.
Aprepitant	Contraceptives	The efficacy of hormonal contraceptives may be reduced. Alternative or back-up methods of contraception should be used during treatment and for 1 month following the last dose of aprepitant.
Aprepitant	Dexamethasone, hydrocortisone, and methylprednisolone	Aprepitant may inhibit the first-pass and systemic metabolism of dexamethasone, hydrocortisone and methylprednisolone, resulting in elevated plasma concentrations of the corticosteroid.
Aprepitant	Pimozide	Aprepitant may inhibit the metabolism of this drug. Concurrent use is contraindicated.
Aprepitant	Terfenadine	Aprepitant may inhibit the metabolism of this drug. Concurrent use is contraindicated.
Aprepitant	Warfarin	Aprepitant may induce the metabolism of warfarin through CYP2C9. The anticoagulant effect of warfarin may be reduced.
Scopolamine	Anticholinergics	The anticholinergic activity of scopolamine may predispose the patient to excessive anticholinergic activity.
Scopolamine	Phenothiazines	Scopolamine may antagonize the effects of phenothiazines by direct central nervous system pathways involving cholinergic mechanisms. An acceleration of phenothiazine gut metabolism has also been postulated.
Scopolamine	Potassium chloride	Anticholinergics may slow gastrointestinal motility, delaying the passage of potassium chloride tablets through the gastrointestinal tract.

Dosage and Administration

Table 8. Dosing and Administration[4-14]

Generic Name	Adult Dose	Pediatric Dose	Availability
Aprepitant	CINV Given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 antagonist, the recommended dose is 125 mg orally 1 hour or 115 mg intravenously 30 minutes prior to chemotherapy treatment (day 1) and 80 mg once daily in the morning on days 2 and 3 PONV 40 mg orally, administered within 3 hours prior to induction of anesthesia	Safety and efficacy in children have not been established.	Capsule: 40 mg 80 mg 125 mg Dose pack: Two 80 mg capsules and one 125 mg capsule Vial: 115 mg
Dronabinol	CINV Initial: 5 mg/m^2 given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day If the 5 mg/m^2 dose is ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose Anorexia (acquired immune deficiency syndrome-related) Initial: 2.5 mg orally twice daily, before lunch and dinner; if adverse effects occur and do not resolve in 1 to 3 days with continued use, reduce dose to 2.5 mg per day before dinner or at bedtime; if clinically indicated and absence of significant adverse effects, dose may be gradually increased to a maximum of 20 mg per day	CINV Initial: 5 mg/m^2 given 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day If the 5 mg/m^2 dose is ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose	Capsule: 2.5 mg 5 mg 10 mg
Nabilone	CINV: Initial: 1-2 mg twice daily to begin 1 to 3 hours prior to the administration of chemotherapy; a dose of 1 or 2 mg the night before chemotherapy may be useful; may be administered 2 or 3 times daily during the entire course of each cycle and, if needed, for 48 hours after the last dose of each cycle; maximum: 2 mg three times a day	Safety and efficacy in children have not been established.	Capsule: 1 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Scopolamine	Motion Sickness Oral: 0.4-0.8 mg 1 hour before exposure to motion, may repeat 3 times daily as needed and as tolerated Patch: apply patch at least 4 hours before the antiemetic effect is required; maximum: 1 patch at any time PONV Patch: apply patch the evening before scheduled surgery; maximum: 1 patch at any time	Safety and efficacy of scopolamine soluble tablets or the transdermal system in children have not been established.	Tablet: 0.4 mg Patch: 1.5 mg (designed to deliver in vivo approximately 1.0 mg of scopolamine over 3 days)

CINV=chemotherapy-induced nausea and vomiting, PONV=postoperative nausea and vomiting

Other Key Facts

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American Society of Clinical Oncology (ASCO): **Guideline for Antiemetics in Oncology: Update (2006)**[15]	• For prophylaxis of acute onset in high emetic risk chemotherapy: any 5-HT_3 receptor antagonist, dexamethasone, and aprepitant are recommended. • For prophylaxis of acute onset in moderate emetic risk chemotherapy: any 5-HT_3 receptor antagonist, dexamethasone, and add aprepitant if the patient is taking anthracycline and cyclophosphamide. • Cannabinoids are not recommended as first-line treatment in patients receiving chemotherapy of high emetic risk and should be reserved for patients who are intolerant or refractory to 5-HT_3 receptor antagonists, NK_1 receptor antagonists, and dexamethasone.
National Comprehensive Cancer Network (NCCN): **Practice Guidelines in Oncology: Antiemesis (2008)**[16]	• For high emetic risk chemotherapy, the combination of aprepitant, dexamethasone and any 5-HT_3 receptor antagonist, with or without lorazepam is recommended. • For moderate emetic risk chemotherapy, the combination of aprepitant, dexamethasone, and any 5-HT_3 receptor antagonist, with or without lorazepam should be used for day one treatment. For days 2-3, aprepitant +/- dexamethasone with or without lorazepam, OR dexamethasone, OR ondansetron, granisetron or dolasetron, for breakthrough emesis, give an additional agent from another class. • For low and minimal emetic risk chemotherapy dexamethasone, OR prochlorperazine, OR metoclopramide +/- diphenhydramine, with or without lorazepam. • For upper abdomen radiation therapy, use ondansetron or granisetron or dexamethasone. • For total body radiation, use ondansetron or granisetron, with or without dexamethasone. • 5-HT_3 receptor antagonists are not recommended for anticipatory nausea and vomiting.
Multinational Association of Supportive Care in	• For the prophylactic treatment of acute emesis in highly emetogenic chemotherapy, a 3-drug regimen is recommended including any 5-HT_3

Clinical Guideline	Recommendations
Cancer (MASCC): **Prevention of Chemotherapy- and Radiotherapy-Induced Emesis: The Results of the 2004 Perugia International Antiemetic Consensus Conference**[17]	receptor antagonist, dexamethasone, and aprepitant. • For the prophylactic treatment of acute emesis in moderately emetogenic chemotherapy, a 3-drug regimen is recommended if the regimen contains anthracycline plus cyclophosphamide and includes any 5-HT_3 receptor antagonist, dexamethasone, and aprepitant.
American Gastroenterological Association Institute: **American Gastroenterological Association Medical Position Statement: Nausea and Vomiting (2001)**[18]	• Motion sickness and related disorders are treated primarily with histamine H_1 and cholinergic receptor antagonists (e.g., scopolamine). • This document does not make specific mention of either of the other two agents reviewed in this class.
The International Anesthesia Research Society: **Consensus Guidelines for Managing Postoperative Nausea and Vomiting (2003)**[19]	• Scopolamine applied the evening before surgery or 4 hours before the end of surgery has been proven effective in studies but its use is limited by side effects and age-related concerns. • Cannabinoids have not been shown to be effective in the treatment of postoperative nausea and vomiting (PONV). • It is important to note that these guidelines were created before the Food and Drug Administration approval of aprepitant for the treatment of PONV.
American College of Obstetricians and Gynecologists: **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy (2004)**[20]	• Pharmacological therapy that is considered safe and efficacious in pregnancy includes antihistamines, phenothiazines, and benzamides (trimethobenzamide).

Conclusions

Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. Physiologic pathways involved in the treatment of nausea and vomiting primarily involve dopamine and serotonin (5-HT). Other receptors which have a lesser role include muscarinic, opiate, histamine H_1, cannabinoid, and neurokinin 1 (NK_1).[48,49] Treatment of chemotherapy-induced nausea and vomiting (CINV) generally involves the use of multiple agents that affect different receptor types, such as a dopamine antagonist, a steroid, and a 5-HT_3 receptor antagonist.[15-17,50] Choice of agents generally depends upon the relative emetogenic potential of the regimen. If one antiemetic regimen is ineffective, it is appropriate to use or add a different agent. If breakthrough emesis or nausea occurs, it is appropriate to add an agent with a different mechanism of action (cannabinoid receptor agonist, cholinergic antagonist, or antihistamine). Aprepitant, the cannabinoids (dronabinol and nabilone) and scopolamine have different mechanisms of action and Food and Drug Administration (FDA)-approved indications. There are no documented head-to-head studies of these agents with regards to antiemetic potential.

Aprepitant has been studied as an additive to standard therapy (a 5-HT_3 receptor antagonist plus dexamethasone) for the prevention of highly or moderately emetogenic CINV. Aprepitant has been

shown to be effective when used with a 5-HT_3 receptor antagonist plus dexamethasone.[21-29] Studies show that a higher proportion of patients receiving the aprepitant regimen had a complete response compared with patients receiving only a 5-HT_3 receptor antagonist plus dexamethasone. National and international guidelines recommend aprepitant as a first-line agent in the prevention of CINV in patients receiving chemotherapy with high and moderate emetic risk.[15-17] Aprepitant is also FDA approved for the prevention of postoperative nausea and vomiting (PONV). When compared to ondansetron, aprepitant was as effective in achieving a complete response during the 0-24 hour postoperative period but was more effective in achieving no vomiting during the 0-48 hour period.[35,36]

Dronabinol and nabilone are FDA approved for the treatment of CINV in patients who have failed to respond to conventional antiemetic treatments. Meta-analyses and head-to-head trials have shown that the cannabinoids were more effective than placebo and some trials reported that they were more effective than prochlorperazine and metoclopramide.[30-34] Dronabinol may improve appetite and weight gain in patients with cancer and acquired immune deficiency syndrome (AIDS); however, megestrol has been shown to be more effective than dronabinol.[44-47,51] Due to the availability of other agents that are more effective and better tolerated than the cannabinoids, dronabinol and nabilone are not considered first-line agents. Both of these agents have a high abuse potential and are regulated under the Controlled Substances Act. There are no head-to-head studies that have compared dronabinol to nabilone for their FDA-approved indications. Dronabinol is available in a generic formulation.

Scopolamine is FDA approved for the treatment of motion sickness. A meta-analysis of 14 studies enrolling over 1,000 patients reported that scopolamine was more effective than placebo in the prevention of motion sickness symptoms.[43] Limited head-to-head studies suggested that scopolamine was at least as effective as antihistamines of which several are available in generic and/or over-the-counter formulations.[42,43] The transdermal patch is also indicated to prevent PONV. A few studies reported that premedication with transdermal scopolamine was as effective as droperidol or ondansetron in preventing nausea and vomiting in the early and late postoperative periods.[38,39] However, the use of transdermal scopolamine was more likely to produce a dry mouth. There are national guidelines that support the use of scopolamine for the treatment of motion sickness and PONV.[18,19]

Recommendations

In recognition of the fact that the miscellaneous antiemetics have a limited role in the management of nausea and vomiting in the outpatient setting, it is recommended that no changes be made to the current approval criteria.

Emend Injection (fosaprepitant) 115 mg requires prior authorization with the following approval criteria:

- The medication will be prescribed by an oncology practitioner.

AND

- The patient requires prevention of nausea and vomiting associated with moderate to highly emetogenic cancer chemotherapy.

AND

- The patient has a medical necessity for the IV administration (i.e. inability to swallow capsules, dysphagia).

AND

- The requested quantity does not exceed one 115 mg vial per course of chemotherapy. Patients with multiple courses of chemotherapy per month will be approved quantities sufficient for the number of courses of chemotherapy.

Emend (aprepitant) 80 mg, 125 mg, Tri-Fold pack is preferred when the following quantity limits are met:

- The medication will be prescribed by an oncology practitioner.

AND

- The patient requires prevention of nausea and vomiting associated with moderate to highly emetogenic cancer chemotherapy.

AND

- The requested quantity does not exceed one 125 mg and two 80 mg capsules OR one Tri-Fold Pack per course of chemotherapy. Patients with multiple courses of chemotherapy per month will be approved quantities sufficient for the number of courses of chemotherapy.

Emend (aprepitant) 40 mg is preferred when the following quantity limits are met:

- The patient requires prevention of postoperative nausea and vomiting.

AND

- The requested quantity does not exceed one 40 mg capsule per surgery or course of anesthesia. Patients with multiple surgeries or courses of anesthesia in a 30 day period will be approved quantities sufficient for the number of surgeries or courses of anesthesia.

Marinol and dronabinol require prior authorization with the following approval criteria:

- The patient has a diagnosis of chemotherapy-induced nausea/vomiting.

AND

- The patient has had a documented side effect, allergy, or treatment failure to at least 2 antiemetic agents, of which, one must be a preferred 5HT3 receptor antagonist. If the request is for Marinol, the patient must additionally have a documented intolerance to generic dronabinol.

OR

- The patient has a diagnosis of AIDS associated anorexia.

AND

- The patient has had an inadequate response, adverse reaction, or contraindication to megestrol acetate. If the request is for Marinol, the patient must additionally have a documented intolerance to generic dronabinol.

Cesamet requires prior authorization with the following approval criteria:

- The patient has a diagnosis of chemotherapy-induced nausea/vomiting.

AND

- The patient has had a documented side effect, allergy, or treatment failure to at least 2 antiemetic agents, of which, one must be a preferred 5HT3 receptor antagonist.

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